UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,192	09/21/2001	Neal Rosen	MSK.P-038	6277

52334 7590 12/12/2005

OPPEDAHL & LARSON LLP - MSK
P. O. BOX 5068
DILLON, CO 80435-5068

EXAMINER	
KIFLE, BRUCK	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 12/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/937,192
Filing Date: September 21, 2001
Appellant(s): ROSEN ET AL.

Marina Larson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 26, 20005 appealing from the Office action mailed July 11, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal. Co-pending Application 09/960,665, however, is drawn to similar subject matter.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed. This appeal brief was filed before a final rejection.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

No evidence is relied upon by the examiner in the rejection of the claims under appeal.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

Claims 12-30 and 32-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling as a method of treating HER-2 expressing cancer using geldanamycin dimer linked by a 4-carbon chain at the 17-positions of each, does not reasonably provide enablement for treating any and all cancers and for destruction of other cells or treating cancers generally using "a chemical compound comprising first and second hsp-binding moieties which bind to the pocket of hsp90 with which ansamycin antibiotics bind, said binding moieties being connected to one another by a linker, wherein the first and second hsp-binding moieties are each an ansamycin antibiotic and retain the ability in the chemical compound to bind to the pocket of hsp90."

The specification does not enable one skilled in the art, to use the invention commensurate in scope with these claims.

See MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical art. In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: The method of use claims are drawn to the destruction of cells expressing a HER-family tyrosine kinase (claim 12) and to a method of treating cancer (claim 13) comprising administering "a chemical compound comprising first and second hsp-binding moieties which bind to the pocket of hsp90 with which ansamycin antibiotics bind, said binding moieties being connected to one another by a linker, wherein the first and second hsp-binding moieties are each an ansamycin antibiotic and retain the ability in the chemical compound to bind to the pocket of hsp90."

2) The state of the prior art: There is no general treatment for cancer and there is no correlation between the assays relied upon by applicants and the ability to treat all cancers. Thus, those assays are not sufficient to enable such claims. The remarkable advances in chemotherapy have seen the development of specific compounds to treat specific types of cancer. The great diversity of diseases falling within the "cancer" category means that it is contrary to current medical understanding that any agent (let alone a genus of compounds) could be generally effective against cancers. Different agents are used for different specific forms of cancer and no single agent is known as a treatment of every single type of cancer.

No compound has shown clinical efficacy against all cancers, thus no *in vivo* or *in vitro* assay could be validated for the identification of such a general agent. The instant specification logically lacks such assay data.

In re Buting 163 USPQ 689 establishes that even clinical tests showing that a compound found to be useful in the treatment of two types of cancers was not sufficient for a much broader range.

See for example, Sreedhar et al. (Biochimica et Biophysica Acta 1697 (2004), 233-242), a review article about inhibitors of Hsp90, Geldanamycin as one Hsp90 inhibitor (page 236) and the limitations of Hsp90 inhibition (page 239). Appellants are going far beyond what is known for the monomer to treat any cancer using any compound of claim 3.

3) The predictability or lack thereof in the art: The invention is pharmaceutical in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be unpredictable. See In re Fisher 166 USPQ 18. Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group where as herein no examples of a diverse nature have been made, much less tested, showing the requisite activity needed to practice the invention.

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no dosage data present to treat a host with any cancer. Only compounds that are GM dimers have been made (see page 6, Table 1) which are much closer to each other than to the remaining scope. Thus, the amount of guidance presented in the specification as to which compounds are sufficiently active to be useful for the claimed uses is nonexistent.

6) The breadth of the claims: The compounds embraced by the claims do not give a reasonable assurance that all or substantial all of them would work. See the testing done in the specification where minor structural differences result in extreme sensitivity. For example, a compound that differs only by the length of the linking carbon chain by two carbons (from 7 to

9) results in one test varies from 70 to 500. This is evidence that the compounds claimed are extremely sensitive to minor structural changes.

The claims are drawn to disorders that are not related and whose treatment using a single compound is unknown. Pancreatic cancer, for example, has proven extremely difficult to treat. Gastric cancer embraces several different types of cancers which includes, Adenocarcinomas (cancers started in the gland cells in the stomach lining), Squamous cells cancers are cancers in the skin-like cells that are mixed with gland cells to make the stomach lining, Lymphomas, sarcomas (cancer that begins in the muscle layer of the stomach is a sarcoma) and Neuroendocrine tumours (cancers that grow in hormone producing tissues, usually in the digestive system). Treatment for each is different.

Regarding claim 12, there is no disclosed benefit taught in destroying all cells, including healthy ones, as claimed in claim 12.

7) The quantity of experimentation need would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

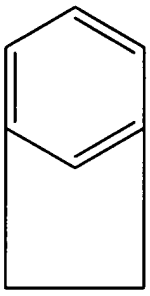
Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

New Grounds of Rejections

Claim Rejections - 35 USC § 112

Claims 3, 4, 6 and 9-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

i) The metes and bounds of the "ansamycin" are unknown. Applicants' argument in the Appeal brief has been fully considered but is not persuasive. Therein, Applicants state, "The ansamycins constitute a class of antibiotics characterized by an aliphatic bridge linking two nonadjacent positions of an aromatic nucleus." This definition includes compounds, such as,



. Is this also an ansamycin? Does the nature of substituents, additional ring fusions; degrees of unsaturation, presence of any other heteroatoms, etc. affect the scope? The point is, there is no definition of an ansamycin antibiotic.

Take for example Geldanamycin, would this still be an ansamycin if the amine were hydrolyzed? How about if there are further substituents or ring fusions? What if the quinone ring is reduced or the ring opened? Can both rings be opened and would this still be an ansamycin?

ii) The nature of the linker is unknown. One skilled in the art cannot say which "linker" is intended. Could another ansamycin be a linker? How about a bond, a ring structure, a peptide, a sugar, an antibody, a cyclic peptide, etc.? In addition, the claim language such as "length of 4 to 7 carbon atoms" is unclear. Are only alkylenes intended or are Applicants relying on the length

of carbon atoms. Appropriate correction is required. The linker should have distinguishing identifying characteristics defined to determine the scope.

iii) The scope of the compounds claimed is undeterminable. The term "bind" in the claims is indefinite. There is no way of knowing whether a given compound would bind. Binding is a process which cannot be observed, merely inferred, which is unreliable. There is no test to determine whether binding is present or not. Furthermore, binding alone is not sufficient to determine the scope of the claims, but binding to the pocket of hsp90 with which ansamycin antibiotics bind is required. Now, the metes and bounds of "ansamycin antibiotic" are not known and the nature of the linker is not known. In addition, hsp90 simply refers to heat-shock proteins with an average molecular weight of 90Kd. This is a family of proteins which consists of Hsp90 alpha and beta, Grp94 and Trap-1. These exist in various mutant forms, and even in these 4, the pockets are not exactly the same.

iv) The phrase "retain the ability" to bind is unclear. Does it mean that the compound is supposed to bind exactly as strongly as the monomer binds or does it mean that it simply needs to bind? Both definitions could be valid, but Appellants need to clarify whether the term "retain" means as strongly or as weakly as the monomer or simply the ability to bind with no regard as to how it accomplishes the binding.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 3, 4, 6 and 9-34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 6, 7, 12, 13 and 15-40 of copending Application No. 09/960,665. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are fully embraced by the claims of 09/960,655.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

(10) Response to Argument

Claims 3, 4, 6 and 9-11 are not rejected for lack of enablement.

Claim 12 is drawn to a method for destruction of cells expressing a HER-family tyrosine kinase. As noted above, healthy cells are included in this claim and there is no benefit in destroying healthy cells.

Appellant's intention may be to destroy those cells that *overexpress* a HER-family tyrosine kinase, but so has not been stated in the claim. Herceptin, a known drug against breast cancer that overexpresses HER2, is not taught to work by destroying cells, but by attaching to HER2 protein receptors on the cell surface, thus, inhibiting the proliferation of human tumor cells that overexpress HER2. Herceptin does not destroy all cells and cell destruction is not what these kinds of compounds do.

Appellants have submitted references showing that the monomeric compounds 17-allylamino-geldanamycin (17-AAG) and Herbimycin (which differs from geldanamycin by replacing the hydroxy group at the 11 position by a methoxy) are efficacious in a variety of tumor types. The claims are, however, drawn to treating any and all cancers. Claims 31-34 are limited to breast cancer, ovarian cancer, pancreatic cancer and gastric cancer. The evidence presented, however, is not commensurate in scope to the breadth of the claims. The specification is not adequately enabling for the scope of the compounds claimed to treat cancers generally. Claims 3, 12 and 13 require compounds comprising a first and second hsp-binding moieties with which ansamycin antibiotics bind. The references do NOT disclose compounds that have the second binding moiety required by the claims.

The rejection here is that all of the compounds made are drawn to a narrow group to treat breast cancer which does NOT give a reasonable assurance that all, or substantially all of them, are useful. The claims are not drawn in terms of a recognized genus but are directed to a more or less artificial selection of compounds.

Table 1 on page 6 of the specification shows that all compounds tested are worse or considerable worse than geldanamycin. Geldanamycin itself does not work and has not been shown to be effective against any cancer and is no longer being investigated.

The references provided cannot overcome this rejection.

Claims 18-20 depend directly or indirectly on claim 13. The narrowing is of the compound; the method is of the same scope as claim 13.

Claim 14 and 21-23 are limited to a cancer which is a HER-positive cancer. The scope of cancer here is not objected to.

Claim 30 is limited to cancer cells which overexpress a HER-family kinase. The scope of cancer here is not objected to.

Claim 24 depends on claim 12 and the rejection above to claim 12 applies. Similarly, claims 25-29 depend on claim 24 and these claims are rejected because of the method of use.

Regarding the lack of definiteness, Appellants arguments do not clarify the scope of an ansamycin antibiotic.

Regarding the linker, Appellants have given no definition of the "linker" intended.

Regarding, the term bind, there is no 35 USC § 103 rejection. Appellants argue that binding refers to the interaction between ansamycin antibiotics with hsp90 and point to the reference of Sebbins et al. (Cell, Vol. 89, 239-250). The reference shows crystal structures of an hsp90-geldanamycin complex. One can conclude that if there is a crystal structure, then one can observe the binding by X-ray crystallographic studies. This, however, could not be done if the compound is liquid or is amorphous. Therefore, if the compound cannot be crystallized, then one cannot observe "binding."

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

This examiner's answer contains a new ground of rejection set forth in section **(9)** above. Accordingly, appellant must within **TWO MONTHS** from the date of this answer exercise one

of the following two options to avoid *sua sponte* **dismissal of the appeal** as to the claims subject to the new ground of rejection:

(1) **Reopen prosecution.** Request that prosecution be reopened before the primary examiner by filing a reply under 37 CFR 1.111 with or without amendment, affidavit or other evidence. Any amendment, affidavit or other evidence must be relevant to the new grounds of rejection. A request that complies with 37 CFR 41.39(b)(1) will be entered and considered. Any request that prosecution be reopened will be treated as a request to withdraw the appeal.

(2) **Maintain appeal.** Request that the appeal be maintained by filing a reply brief as set forth in 37 CFR 41.41. Such a reply brief must address each new ground of rejection as set forth in 37 CFR 41.37(c)(1)(vii) and should be in compliance with the other requirements of 37 CFR 41.37(c). If a reply brief filed pursuant to 37 CFR 41.39(b)(2) is accompanied by any amendment, affidavit or other evidence, it shall be treated as a request that prosecution be reopened before the primary examiner under 37 CFR 41.39(b)(1).

Extensions of time under 37 CFR 1.136(a) are not applicable to the TWO MONTH time period set forth above. See 37 CFR 1.136(b) for extensions of time to reply for patent applications and 37 CFR 1.550(c) for extensions of time to reply for ex parte reexamination proceedings.

Respectfully submitted,

Bruck Kifle, Ph.D.

A Technology Center Director or designee must personally approve the new ground(s) of rejection set forth in section (9) above by signing below:

Conferees:

Mr. James Wilson
SPE Art Unit 1624/ Director's designee

Dr. Mark Berch
Primary Examiner, Art Unit 1624

December 8, 2005